522 Rec'd PCT/PTO 0 6 DEC 1999

FORM PTO-1390 (REV 11-98)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER 3687-2
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 09/445218 Unassigned
INTERNATIONAL APPLICATION NO. PCT/EP98/03496	INTERNATIONAL FILING DATE 4 June 1998	PRIORITY DATE CLAIMED 5 June 1997

TITLE OF INVENTION
DIPHENYL-TRIAZOLE DERIVATIVES AND THEIR USE AS ANTI-GESTATIVE, IMMUNO-SUPPRESSANT AND ANTI-TUMORAL AGENTS

APPLICANT(S) FOR DO/EO/US
ROSSI, Carla

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has **NOT** expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (U.S.C. 371(c)(3)).

9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. To 16. Below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☐ Other items or information.

Rec'd PCT/PTO 06 DEC 1999

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
Unassigned 09/44 5218	PCT/EP98/03496	3687-2

17. ☒ The following fees are submitted:

	CALCULATIONS	PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):

-- Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $970.00

-- International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $840.00

-- International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2) paid to USPTO $760.00

-- International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $670.00

-- International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $96.00

ENTER APPROPRIATE BASIC FEE AMOUNT = $ 970.00

Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)). $ 0.00

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE			
Total Claims	26	-20 =	6	X	$18.00	$	108.00
Independent Claims	1	-3 =	0	X	$78.00		0.00
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)				+$260.00		$	0.00
				TOTAL OF ABOVE CALCULATIONS =		$	**1078.00**
Reduction by ½ for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).							0.00
				SUBTOTAL =		$	**1078.00**
Processing fee of $130.00, for furnishing the English Translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+			0.00
				TOTAL NATIONAL FEE =		$	**1078.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property				+		$	0.00
Fee for Petition to Revive Unintentionally Abandoned Application ($1,210 – Small Entity Fee = $605)						$	0.00
				TOTAL FEES ENCLOSED =		$	**1078.00**
						Amount to be: refunded	$
						charged	$

a. ☒ A check in the amount of $1078.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 14-1140 in the amount of $_____ to cover the above fees. A duplicate copy of this form is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-1140. A duplicate copy of this form is enclosed.

d. ☐ The entire content of the foreign application(s), referred to in this application is/are hereby incorporated by reference in this application.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SIGNATURE

SEND ALL CORRESPONDENCE TO:

NIXON & VANDERHYE P.C.
1100 North Glebe Road, 8th Floor
Arlington, Virginia 22201
Telephone: (703) 816-4000

Arthur R. Crawford
NAME

25,327 **December 6, 1999**
REGISTRATION NUMBER Date

386512

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

ROSSI, Carla Atty. Ref.: 3687-2

Serial No. **Unassigned** Group:

Filed: **December 6, 1999** Examiner:

For: **DIPHENYL-TRIAZOLE DERIVATIVES AND THEIR USE AS ANTI-GESTATIVE, IMMUNO-SUPPRESSANT AND ANTI-TUMORAL AGENTS**

* * * * * * * * * * *

December 6, 1999

Assistant Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

Sir:

Please amend the above application as follows:

IN THE CLAIMS

Claim 19, lines 1-2, delete "claims 17 and 18.," and replace by --claim 17--.

Claim 20, lines 1-2, delete "claims 17 and 18.," and replace by --claim 17--.

Claim 21, lines 1-2, delete "claims 17 and 18.," and replace by --claim 17--.

Claim 23, lines 1-2, delete "claims 17 and 22.," and replace by --claim 17--.

Claim 24, lines 1-2, delete "claims 17 and 22.," and replace by --claim 17--.

Claim 25, lines 1-2, delete "claims 17 and 24.," and replace by --claim 17--.

REMARKS

The above amendments have been made to multiple dependent claims and reduce initial filing fees.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Arthur R. Crawford
Reg. No. 25,327

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OMB No. 0651-0011 (12/31/86)

Applicant or Patentee: Carla Rossi — Attorney's Dkt. No. 3687-2

Serial or Patent No.: 09/445,218

Filed or Issued: January 28, 2000

For: DIPHENYL-TRIAZOLE DERIVATIVES AND THEIR USE AS ANTI GESTATIVE, IMMUNO-SUPPRESSANT ETC.

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS [37 19(f) and 1.27(c)] - SMALL BUSINESS CONCERN

I hereby declare that I am

☒ the owner of the small business concern identified below:
an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN Geange Ltd.

ADDRESS OF CONCERN 20 Clanwilliam Terrace, Dublin 2, IE

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled:

DIPHENYL-TRIAZOLE DERIVATIVES AND THEIR USE AS ANTI-GESTATIVE, IMMUNO-SUPPRESSANT AND ANTI-TUMORAL AGENTS

by inventors CARLA ROSSI described in

☐ the specification filed herewith.

☒ application Serial No. 09/445,218, filed JANUARY 28, 2000

☐ patent No. _____, issued _____

If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor who could not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities (37 CFR 1.27)

☐ Name _____
Address _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

Name _____
Address _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

I acknowledge the duty to file, in this application of patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. [37 CFR 1.28(b)]

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Adelio LARDI

TITLE OF PERSON OTHER THAN OWNER Legal Representative of Geange Ltd

ADDRESS OF PERSON SIGNING Via Cantonale 19 - Lugano CH

SIGNATURE _____ DATE Dec. 22, 1999

DIPHENYL-TRIAZOLE DERIVATIVES AND THEIR USE AS ANTI-GESTATIVE, IMMUNO-SUPPRESSANT AND ANTI-TUMORAL AGENTS

OBJECT OF THE PRESENT INVENTION

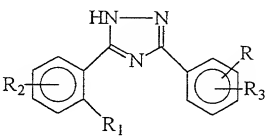
Objects of the present invention are nitrogen heterocyclic aromatic derivatives and their use as anti-gestative, immunosuppressant and anti-tumoral agents.

Object of the present invention is also a procedure for the preparation of nitrogen heterocyclic aromatic derivatives.

Object of the present invention is again a pharmaceutical composition which contains, as active principle, at least one heterocyclic aromatic according to the present invention.

STATUS OF THE TECHNIQUE

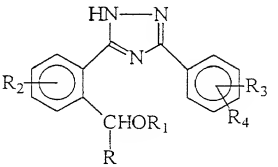
Chemical classes of compounds endowed with anti-gestative activity are known, more specifically BE 866,728 reports a class of 3, 5-diphenyl-1H-1, 2, 4 triazoles of the



following general formula:

where R_1 is an alkyl group C_1-C_4 .

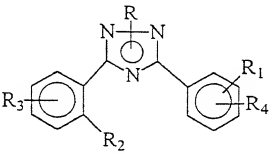
EP11129 reports 1, 2, 4 triazoles derivatives of the following general structure:



where R is hydrogen or methyl and R_1 is hydrogen or an alkyl group C_1-C_4 , or R_1 and R_2 together form an additional bond between the carbon and oxygen atoms.

BE 879,732 reports a class of compounds showing the following general structure:

where, among the other possible substitutions, R is an



hydrogen or a R_5-CO group where R_5 is chosen among alkyl C_1-C_4, alkenyl C_2-C_4 and alkinyl C_2-C_4 , whereas R_2 is a -$CH(R_7)OR_8$ where R_7 is an hydrogen or methyl and R_8 is like R_5-CO.

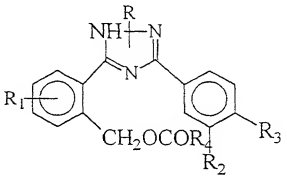
In the above mentioned disclosed documents, the pharmacological data show how these compounds display a high anti-gestative activity after repeated parenteral administrations (daily up to 5 consecutive days). The literature describes the compound 3-(2-ethyl-phenyl)-5-(3-methoxy-phenyl)-1H-1,2,4-triazole, also identified by the code DL 111-IT (Reviews on Drug Metabolism & Drug Interactions, Vol. IV, N. 2&3, 1982, A. Assandri, A: Omodei-Sale', G. Galliani).

The mentioned DL 111-IT, reported in BE 879,732, did show an interesting anti-gestative activity in all the investigated animal species including the mouse, the rat, the hamster, the dog and monkeys. DL 111-IT has been proposed as anti-gestative agent for human use.

These previously disclosed anti-gestative compounds, including the compound DL 111-IT, when tested according to a protocol which foresee a single dose parenteral treatment, displayed their activity at doses much higher than those required by multiple dose regimens.

EP0080053 describes 3, 5 diphenyl-1H-1, 2, 4 triazole derivatives that, as compared to the previously reported derivatives, have been structurally modified in order to obtain a high anti-gestative activity after a single-dose parenteral administration by subcutaneous and intramuscular route.

The compounds described in EP0080053 have the following general structure:



where, R is chosen between hydrogen and R_5CO-, where R_5 is a saturated or non-saturated aliphatic C_1-C_{20} hydrocarbon chain, R_1, R_2 and R_3 are chosen among hydrogen and short-chain alkyl or alkoxyl, or R_1 and R_2 together form a methylendioxy group, R_4 is a saturated or non-saturated aliphatic C_1-C_{20} hydrocarbon group.

The above mentioned derivatives, when given by single dose to rodents, displayed a high anti-gestative activity. This activity was however shown to be highly

species-specific. Actually, while in rodents it was very high, in the higher mammal species, like the dog, the anti-gestative activity markedly decreased, due to a too slow hydrolysis rate of the administered products that undergo metabolism before the active principle become bioavailable.

OBJECTIVES OF THE INVENTION

Objective of the present invention is to make available nitrogen heterocyclic aromatic derivatives endowed with high anti-gestative activity when administered as single dose to different animal species including higher mammals and man.

Objective of the present invention is also to make available nitrogen heterocyclic aromatic derivatives endowed with high immuno-suppressant activity.

Again, objective of the present invention is to make available nitrogen heterocyclic aromatic derivatives endowed with non species-specific anti-gestative, immuno-suppressant and anti-tumour activity.

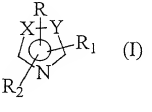
Again, objective of the present invention is to make available nitrogen heterocyclic aromatic derivatives endowed with a sustained duration of action, thus able to display the desired activity by a single-dose treatment

(anti-gestative activity) or by multiple dose treatments with wide inter-administration time intervals (immuno-suppressant and anti-tumour activities).

Objective of the present invention is also to make available a pharmaceutical formulations, containing at least one nitrogen heterocyclic aromatic derivative as active principle, easy to be administered, well tolerated and able to allow a high therapeutic index.

DESCRIPTION OF THE INVENTION

These and other objectives with further advantages which are clarified in the description below, are obtained by the nitrogen heterocyclic aromatic derivatives having the following general formula:



(I)

where:

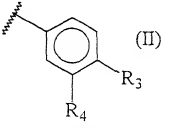
-when X=Y, X, Y=N;

-when X≠Y, X, Y=N, C, CH;

-R is chosen between hydrogen, -COR_8 where R_8 is a saturated or non-saturated C_1-C_{10} aliphatic hydrocarbon,

or R represents any other group able to form a bond with a nitrogen atom;

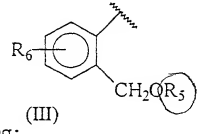
- R_1 has the following general formula:



(II)

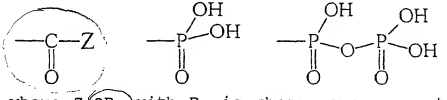
where R_3 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, R_4 is chosen among hydrogen, alkyl or alkoxyl C_1-C_{10}, or R_3 and R_4 together form a methylendioxy group;

- R_2 has the following general structure:



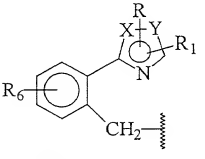
(III)

where R_5 is chosen among:



where $Z{=}OR_7$ with R_7 is chosen among a saturated or non-saturated, linear or branched C_1-C_{20} aliphatic

hydrocarbon, or is chosen according to the following formula:



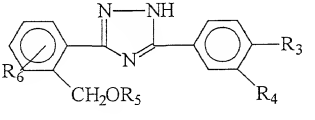
(XII)

where R, R_1, X and Y are defined as above and R_6 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, or Z is chosen equal to NHR_8 where R_8 is a linear or branched C_1-C_{20} alkyl chain. Mentioned R_1 and R_2 are never located on two adjacent atoms of the heterocyclic aromatic ring.

According to the present invention, the term saturated or non-saturated aliphatic hydrocarbon means a linear or branched alkyl, alkenyl or alkinyl chain which contains one or more double or triple bonds. Always according to the present invention, the term alkyl or alkoxyl means a linear or branched alkyl or alkoxyl group.

Namely, the mentioned nitrogen heterocyclic aromatic derivative of formula (I) is a derivative of imidazole and 1H-1, 2, 4-triazole respectively:

According to the present invention, the mentioned derivative of formula (I) is a triazole derivative having the following general formula:

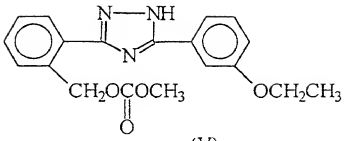


(IV)

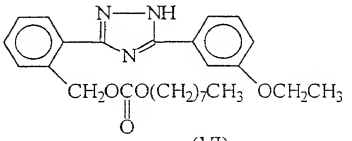
where X=Y=N, while the other substituents are defined as for the derivative of formula (I).

Of particular interest are those derivatives of formula (IV) where R_6 is hydrogen, R_4 is $-OCH_3$ or $-OCH_2CH_3$, R_3 is hydrogen, R_5 is chosen equal to COZ where $Z=OR_7$ with R_7 as a saturated linear aliphatic C_1-C_{12} hydrocarbon.

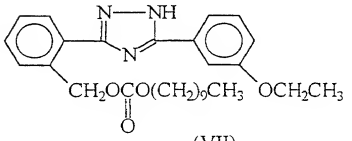
Always according to the present invention, of particular interest were those derivatives having the following formulas:



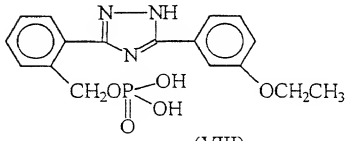
(V)



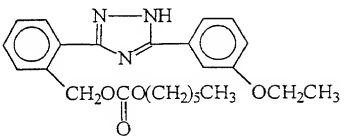
(VI)



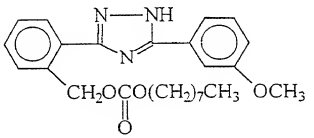
(VII)



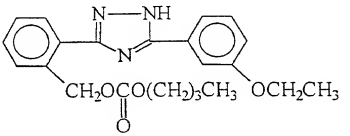
(VIII)



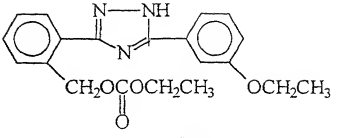
(XVI)



(XIII)

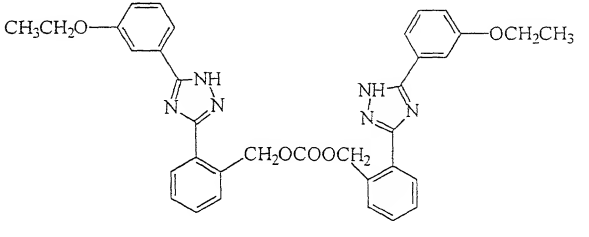


(XIV)

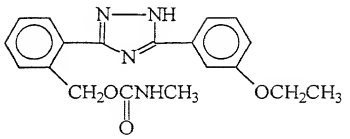


(XV)

In addition according to the present invention, of particular interest were the two derivatives having the following formulas:



(XVII)



(XVIII)

As reported in the literature, see Potts K.T , J: Chem. Soc. 3451, (1954) and Potts K.T., Chem. Rew. 61, 99 (1961), Kubota and Uda, Chem. Pharm. Bull. 23(5), 955 (1975), due to the high mobility of the hydrogen atoms of 1, 2, 4-triazoles, compounds of formula (I) of the present invention where X=Y=N, are to be regarded as a mixture of two tautomeric forms, i.e. those in which the hydrogen atom is located on one or the other of the two adjacent nitrogen atoms of the triazole ring. Depending on the nature of the substitutes at the 3 and 5 positions, a form may predominate on the other one. Consequently, both mentioned tautomeric forms must be considered as part of the present invention. It is known that tautomeric forms rapidly exchange in between and consequently behave as a dynamic equilibrium.

Anyway, throughout the whole description and claims relative to the present invention, 3, 5 diphenyl-1H-1, 2,

4-triazoles according to the present invention, will be numbered as reported above for derivative (V).

The derivatives of the present invention are provided of anti-gestation, immuno-suppressive and anti-tumour activities Particularly, the anti-gestative activity is displayed by a single dose regime and it does not requires a prolonged treatment. Furthermore, these derivatives show high therapeutic indexes, since a remarkable efficacy is achieved at doses much lower than the toxic ones able to induce undesirable adverse events. The compounds of the present invention of formula (I), when administered as a single parenteral injection displayed more than one pharmacological activity, namely:

(a) they have proven to be highly effective in terminating pregnancy in rodent and non-rodent animal species;

(b) they have proven to be highly effective in reducing both the humoural and cellular immunological response in animal models predictive for the pharmacological activity in humans

(c) in addition, the compounds of the present invention while lacking of effectiveness in different tumour models, showed a specific marked activity on an model of human chorio-carcinoma transplanted in nude mice.

The different pharmacological activities displayed by the derivatives object of the present invention, are attributable to a common mechanism of action.

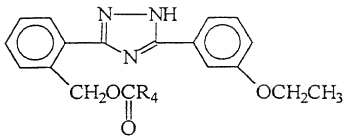
The reference model which explains this multiple pharmacological action is an atypical rapidly proliferating cell system, the placenta.

As reported by Aitken, Beaconsfield and Ginsher in their comprehensive review ▒ Origin and formation of the placenta▒ , this system, during its early stage of development, has strong similarities to tumour (1). Among these in particular, the placenta is tolerated by the maternal host due to an alteration of the immune responsiveness with no inflammatory response to blastocyst and/or throphoblast invasion.

Biochemical studies on placental tissue, during the early post-implantation period, demonstrated that the contra-gestational activity of 3,5 diaryl-1H-1,2,4-triazoles occurs through a selective action on the decidual and throphoblastic cells. Reasonably, this selective anti-proliferative action can also account for the activity of 3,5 diaryl-1H-1,2,4-triazoles against a gestational tumour like chorio-carcinoma. Finally, the immuno-suppressant response, which closely relates to the contra-gestational potency of 3,5 diaryl-1H-1,2,4-

triazoles , may either be the early or the late response of the primary biochemical alterations.

The derivatives object of the present invention are characterised by the presence of an easily hydrolysed bond through non species-specific enzymatic reactions occurring on R_5 group ; this hydrolysis allows the release of the active principle that can display its *in vivo* action. The characteristic bond of R_5 group present in the derivatives object of the present invention, is different from the bonds described in the already disclosed derivatives, and it can be hydrolysed according to different mechanisms of reaction. Because of these properties , unlike the compounds already disclosed, the compounds objective of the present invention are also effective in higher mammal species, including humans. With the aim of evaluating whether inter-species difference could exist in the enzymatic reactions of the ester bond, compounds (XV), (XIV, VI) ad some known derivatives described in EP0080053 (compounds A ,B and C) have been tested *in vitro:*



where when R_4 is chosen as $-C_3H_7$ the compound is named A; where when R_4 is chosen as $-C_7H_{15}$ the compound is named B;

Where when R_4 is chosen as $-C_8H_{23}$ the compound is named C;

These compounds dissolved in an ethanol mother solution, when incubated in diluted (1:4 v/v, with saline, 0.9% NaCl) rat, dog and human serum at a 10^{-5} M concentration for 1 hour at 37°C underwent enzymatic hydrolysis. The hydrolysis rates, expressed as nMoles/hour of the active principle formed, i.e. 3-(2-hydroxymethyl-phenyl)-5-(3-ethoxyphenyl)-1H-1,2,4 triazole, corresponding to the compound described in EP0080053, were measured. The values obtained, reported in Table 1, show how, in the higher species considered, i.e. the dog and man, the known products A, B and C undergo hydrolysis very slowly whereas compounds (XIV), (XV) and (VI), are rapidly metabolised both by rat, dog and human serum.

TABLE 1 : *HYDROLYSIS RATE OF SELECTED 3-(3-ETHOXYPHENYL)-5-(2-ACYL-CARBOXYMETHYL-PHENYL)-1H-1,2,4 TRIAZOLES, COMPOUNDS (XV), (XIV) and (VI) AND SELECTED 3-(3-METHOXYPHENYL)-5-(2-ACYLOXYMETHYL-PHENYL)-1H-1,2,4 TRIAZOLES, COMPOUNDS (A), (B) AND (C)*

COMPOUND	Rate of Hydrolysis (nmoles/hour)		
	RAT	DOG	MAN
(XV)	≥ 120	≥ 120	≥ 120
A	≥ 120	16	12
(XIV)	≥ 120	≥ 120	≥ 120
B	≥ 120	3	2
(VI)	≥ 120	≥ 120	≥ 120
C	≥ 120	< 0.5	< 0.5

Since the metabolic attack (de-alkylation) of these structures, occurring in position meta with respect to the substituent R_1 of structure (II), gives rise to inactive or poorly active metabolites, a too slow hydrolysis of compounds A, B and C will lead to a marked reduction of the activity of these molecules in the higher species. On the contrary, as already mentioned, derivatives of the present invention of formula (I), can be usefully used in higher mammal species including the dog and man. The compounds of the present invention

actually represent a class of new non-hormonal, non-prostaglandin, like, post-coital, post-implantation anti-fertility agents particularly useful for terminating pregnancy in mammals following a single dose treatment at very low doses.

The pregnancy-terminating activity of the compounds of the present invention has been assessed by carrying out experiments in rats and dogs.

In particular, female Sprague Dawley rats weighing 200-230 g. were mated and the presence of sperm was detected, was considered day one of pregnancy.

Pregnancy was later confirmed at the time of autopsy by the presence of implantation sites in the uterus.

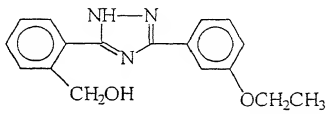
Test compounds dissolved in sesame oil containing 20% benzyl benzoate (or suspended if insoluble), were administered subcutaneously, in a single injection, on day 7 of gestation. The animals were then autopsied on day 16 of pregnancy and the uteri were examined for evidence of pregnancy (implantation sites, foetal resorption or live foetuses), haemorrhage, and evidence of abnormalities of the uterus, placenta or foetuses, *for reference see G. Galliani et al. Contraception, 23, 163-180 (198)*..

The compounds were tested at different doses in order to study the dose-activity relationship and their activity,

reported below in Table 2, has been expressed as ED_{50} values.

These values identify the dose levels which terminate pregnancy (absence of live foetuses) in 50% of the treated animals. For comparison purposes, the ED_{50} of some related triazoles previously disclosed (Belgian patents 866,728 and 879,732 and European patent application publication No. 11,129), are reported.

In particular compound D (active principle), has the following structural formula:



and it has been prepared as described in EP 11129, while compound E, prepared as described in BE 879732 and identified as DL111-IT, has the following formula:

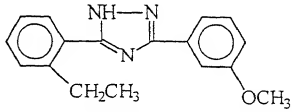


TABLE 2 : *PREGNANCY TERMINATION ACTIVITY IN S.D. RATS AFTER A SINGLE SUBCUTANEOUS INJECTION AT DAY 7 OF GESTATION*

Compound	ED_{50} mg/kg	ED_{50} μmoles/kg
(XV)	15	27.2
(XIV)	8	20.3
(XVI)	5	11.8
(VI)	2	4.4
D*	16	54.6
E**	35	125.4

*5-(2-Hydroxymethylphenyl)-3-(3-ethoxy-phenyl)-1H-1, 2, 4-triazole described in the European patent application Publication No. 11, 129

**5-(2-Ethylphenyl)-3-(3-methoxyphenyl)-1H-1, 2, 4-triazole, DL 111-IT, described in example 24 of Belgian patent 879, 732

The results obtained show how the compounds of formula (I) object of the present invention administered by a single parenteral injection are much more effective of the two compounds previously disclosed taken as reference.

Acute toxicity studies did show as the lethal doses of compounds (VI), LD_{50} > 500 mg/kg, are of three order of magnitude higher than those anti-gestative.

In another experiment carried out in Beagle bitches (0.9 - 4.5 y, 7 - 12.5 kg), compound (VI), i.e. 3-(2-decanoyl-oxymethylphenyl)-5-(3-ethoxy phenyl)-1H-1, 2, 4-triazole, when administered as a single intramuscular dose between the day of mating and the 25th day of gestation was found to be highly effective and very well tolerated.

The compound was given intramuscularly in one depot site of the thigh muscle of the right hind leg dissolved in sesame oil at the dose of 5 mg/kg (11.1 *µmoles/kg* , 40 mg/mL, 0.2 mL/kg). The anti-gestative effectiveness was ascertained by exploratory laparatomy examining uterine horns where the presence of live or dead foetuses was deduced from the dimension and appearance of each uterine swelling, for methodological reference *see G.Galliani et al.,J. Small Animal Practice, 25, 211-222 (1984).*

TABLE 3 : CONTRAGESTATIONAL EFFECT OF COMPOUND (VI), GIVEN AS SINGLE I.M. DOSES BETWEEN THE DAY OF MATING AND THE 14TH DAY OF GESTATION.

Administration (days of gestation)	**Dose** *(µmoles/kg)*	**No of bitches**	**Pregnancy arrest (%)**

15	5 (11.1)	5	80
20	5 (11.1)	5	100
25	5 (11.1)	5	100

The compounds of the present invention displayed significant immuno-suppressive activity on both humoral and cellular immunity when administered during the inductive phase of the immuno response, i.e. soon after antigen challenge. In experimental models of auto-immunity and skin transplantation they were able to reduce auto-antibody production as well as to prolong the skin graft survival.

The immuno-suppressant activity of the compounds of the present invention was assessed by carrying out experiments in mice.

In detail, the *Antibody Response to Sheep Red Blood Cells (SRBC) and to Lipo-polysaccharide (LPS)*, was studied in B6D2F1 mice injected intravenously 10^8 SRBC (day 0). Direct (IgM) and indirect (IgG) plaque forming cells (PFC) were evaluated in the spleen 4 and 10 days later, *Jerne et al. Science 140, 405 (1963) and Dresser and Wortis, Nature, 208, 859(1965)*.

Indirect PCF were developed with rabbit anti-serum to mouse gamma globulin.

B6D2F1 mice were immunised with 20 µg LPS intraperitoneally. Four days later, PCF were determined in the spleen by SRBC coated with LPS, *Moller, Nature, 207, 1166(1965)*.

TABLE 4 : *IgM ANTIBODY RESPONSE TO SRBC AND LPS AFTER SINGLE TREATMENT WITH COMPOUND (VI) COMPARED TO THAT OBTAINED AFTER MULTIPLE TREATMENT WITH THE REFERENCE COMPOUND E (see Mistrello et al., 1985)*

COMPOUND	ANTIGEN	DAY OF DOSING	DOSE (µmoles/Kg/day)	PCF/spleen $.10^{-3}$ (mean ± S.D.)
(VI)	SRBC	0	vehicle	124 + 18
	SRBC	0	8.60	12 + 3*
	LPS	0	vehicle	10 + 2
	LPS	0	8.60	3 + 1*
E	SRBC	0,1,2,3	vehicle	115 ± 20
	SRBC	0,1,2,3	17.92	7 ± 2*
	LPS	0,1,2,3	vehicle	11 ± 2

	LPS	0,1,2,3	17.92	4	±
				1*	

* p<0.01

TABLE 5 : *IgG ANTIBODY RESPONSE TO SRBC AFTER SINGLE TREATMENT WITH COMPOUND OF (VI) COMPARED TO THAT OBTAINED AFTER MULTIPLE TREATMENT WITH THE REFERENCE COMPOUND E (see Mistrello et al., 1985)*

COMPOUND	DAY OF DOSING	DOSE (μmoles/Kg/day)	PFC/SPLEEN.10^{-3} (mean + S.D.)
(VI)	0	vehicle	24 + 3
	0	2.15	3 + 3*
E	0 - 3	vehicle	26 + 4
	0 - 3	3.58	4 + 3*

Delayed Type hypersensitivity (DTH), was carried out in C57B1/6 mice administered subcutaneously 2 x 10^8 SRBC emulsified in complete Freund's adjuvant. Ten days later an eliciting dose of 10^8 SRBC was inoculated into a footpad. The DTH reaction was recorded 24 hours later by measuring the footpad swelling *(Kerckhaert et al, Cell Immunology, 29, 232,(1977)*.

TABLE 6 : *EFFECT ON DTH AFTER SINGLE TREATMENT WITH COMPOUND OF COMPOUND (VI) COMPARED TO THAT OBTAINED AFTER MULTIPLE TREATMENT WITH THE REFERENCE COMPOUND E (see Mistrello et al., 1985)*

COMPOUND	DAY OF DOSING	DOSE (µmoles/Kg/day)	FOOTPAD SWELLING UNITS* (Mean + S.D.)
(VI)	0	vehicle	11.4 + 3.7
	0	8.60	5.2 + 1.2**
E	0,1,2,3,4,5,6,7,8	vehicle	10.1 + 3.3
	0,1,2,3,4,5,6,7,8	17.92	4.1 + 1.4**

*1 unit = 0.1 mm, **p< 0.01

For the *Skin Grafting*, fitted pinch grafts of skin from C3H ($H\text{-}2^k$) donor mice were transplanted onto C57B1/6 ($H\text{-}2^b$) recipient mice (Mistrello et al,. 1984). Bandages were removed 7 days later and graft were scored daily by microscopy. Rejection was recorded when no viable epidermis remained. The median survival time (MST) of the

grafts, measured as days, was calculated according to Litchfield (1949).

TABLE 7 : *EFFECT ON SKIN GRAFT SURVIVAL TIME (MST) AFTER 1 WEEKLY TREATMENT WITH COMPOUND (VI) COMPARED TO THAT OBTAINED AFTER MULTIPLE TREATMENT WITH THE REFERENCE COMPOUND E (see Mistrello et al., 1985)*

COMPOUND	DAYS OF DOSING	DOSE (µmoles/Kg/day)	MST , days (mean + S.D.)
(VI)	-1, 7	vehicle	10.7 + 0.4
	-1, 7	17.20	15.1 + 0.6*
E	-1,1,3, 5, 7, 9,11	vehicle	11.0 + 0.4
	-1,1,3, 5, 7, 9,11	89.61	14.7 + 0.7*

* $p < 0.01$

Finally, the compounds of the present invention are endowed with a high and specific anti-tumour activity as demonstrated on an in vivo test against human choriocarcinoma.

In particular compound of example 5 was highly effective in inhibiting the growth of a human chorio-carcinoma transplanted into nude mice. The potency of the tested compound was even higher than that displayed by methotrexate, the choice drug in the therapy of chorio-carcinoma.

Noteworthy, choriocarcinoma is a gestational tumor derived from trophoblastic cells, which, toghether with decidual cells, was suggested as the target site of the anti-proliferative action of 3, 5 diaryl-s-1,2,4 triazoles (Galliani et al. 1986).

For their use in suppressing the immunological response, in terminating pregnancy, and in treating chorio-carcinoma, the compounds of the present invention are embodied into topical, transdermal and injectable dosage forms to be administered epicutaneously or parenterally, i.e. subcutaneously, intramuscularly or intravenously. Such composition are formulated using proper transdermal delivery systems (epicutaneous dosing), aqueous (intravenous dosing) or non-aqueous vehicles (epicutaneous, subcutaneous and intramuscular dosing).

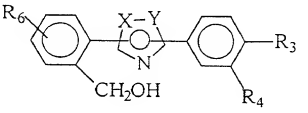
As examples of such systems/vehicles, the following can be considered for epicutaneous, subcutaneous and intramuscular dosing : oils of vegetable origin or fatty

esters such as sesame oil, corn oil, peanut oil, cotton seed oil, and ethyl oleate can suitably be employed.

Other oily vehicles may as well be used provided that they are safe in the volume administered and do not interfere with the therapeutic efficacy of the preparation. As known to the art skilled man, these preparations may also contain anti-microbial agents, to prevent growth of micro-organisms in the preparation, and antioxidants, essentially to prevent the development of rancidity of the oily vehicle.

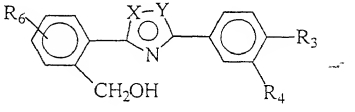
These dosage forms in general contain from 1 to 10% (w/v) of at least one derivative of formula (I) object of the present invention, where the optimum dose/volume ratio depends on the selected dose and the species and size of the animal/subject to be administered.

As an example, the compounds of the present invention can be advantageously prepared starting from a derivative (IX) of the following chemical formula:



(IX)

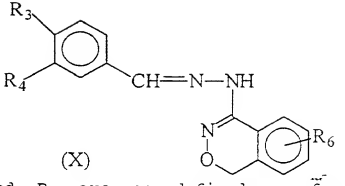
More particularly, when substituents R_1 and R_2 are in position 3 and 5 respectively, the corresponding derivative (XI) has the following chemical formula:



(XI)

The above mentioned derivative of formula (XI), used as starting materials in the process of the present invention, is prepared according to different procedures already reported by the literature. In particular when X=Y=N, the corresponding derivative (XI a) can be advantageously prepared as described in EP11129. In this case the method

This method consists in the rearrangement of hydrazones of substituited benzaldehydes with 4-hydrazino-1H-2,3-benzoxazines of formula (X)



(X)

wherein R_1, R_2 and R_3 are as defined as for the derivatives of formula (I).

This rearrangement simply occurs by refluxing the hydrazone III in a high boiling inert organic solvent, such as for instance, xylene, N,N-dimethylformamide, and halogenated aromatic hydrocarbons, for about 30 minutes and then recovering the compound II by filtration.

Another suitable method for the preparation of the 2-hydroxymethyl-phenyl derivatives of formula (XI a), consists in the oxidation of the corresponding 2-methylphenyl triazoles, either directly to the alcohol (XI a) or to the corresponding carboxylic acid followed by a reduction of this latter to the alcohol(XI a).

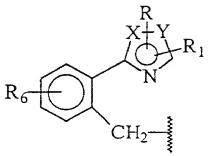
In the former case, ceric ammonium nitrate or silver (II)oxide are the oxidising agents which may be suitably employed, while in the latter, the oxidative step is carried out with any of the several oxidisers known in the art to transform a methyl group on an aromatic ring to a carboxylic group, such as permanganate, nitric acid,

and dichromate, and the reductive step in easily performed with a metal hydride.

Alternatively, the starting compounds of formula II can be prepared by following the process described in EP80053.

Referring to compounds of formula (I), object of the present invention, the procedure for their preparation starting from the corresponding derivative of formula (IX) varies depending whether the substituent R is hydrogen or a group R_8-CO wherein R_8 has the same meaning as above in relation to derivatives of formula (I).

When R is hydrogen, the derivative of formula (IX) is prepared according to different procedures already reported by the literature, in equimolar ratio with phosgene ($COCl_2$) and the resulting chloro-carbonate is left to react with a derivative Z where Z=OR_7 and R_7 is chosen among a saturated or non-saturated, linear or branched aliphatic hydrocarbon C_1-C_{20} , or is chosen according to the following formula:



(XII)

where R, R_1, X and Y are defined as above and R_6 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, or Z is chosen equal to NH-R_8 where R_8 is a linear or branched C_1-C_{20} alkyl chain.

The derivative of formula (I) where R is chosen as hydrogen, can be successively separated from the possible by-products formed during the reaction with phosgene. Phosgene to use is commercially available already dissolved in appropriate solvents.

Following this procedure can be then prepared for example, derivatives (V), (VI) and (VII) of the present invention.

Alternatively, when have to be synthesised derivatives of formula (I) where R_7 is chosen as (XII), asymmetric carbonates, or when R_7 is chosen as saturated or unsaturated, linear or branched C_1-C_{20} aliphatic hydrocarbon, derivative of formula (IX) can undergo

reaction according to the following general scheme, in detail:

⇒both for the intermediates preparation (alcoholate and imidazolide) and for the end carbonate product, an inert solvent is chosen, i.e. chloroform, dichloromethane, tetrahydrofuran:

⇒alcoholate preparation is carried out on the selected alcohol using as base NaH or matallic Na either in catalytic or stoichiometric amounts, temperature can be between 0°C and 60°C (optimal room temperature), while reaction time ranges between 30 min to 12 hours (optimal 1 hour);

⇒the synthesis of the imidazolide of the second alcohol is carried out using as reagent carbonyl-diimidazole with temperature between 0°C and 60°C (optimal, room temperature), while reaction time ranges between 30 min to 12 hours (optimal 1 hour);

⇒the synthesis of the end carbonates products is carried out by mixing properly the solutions of the alcoholate and of the imidazolide for a time of 6 to 24 hours (optimal 12 hours) at a temperature between 0°C and 60°C (optimal, room temperature).

Merely as an example, not limiting the present invention, a general method for the synthesis of derivatives of formula (I), where R and R_3 are chosen as hydrogens, R_4 is chosen as ethoxyl, R_5 is chosen as $COOR_7$ where R_7 is a linear or branched C1-C20 alkylic chain, is hereafter described:

Example 1

A 50 mL solution of 3-(2-(hydroxymethyl)phenyl)-5-(3-ethoxyphenyl)-1H-1, 2, 4 triazole (3g, 10 mmoles) in tetrahydrofuran, at room temperature, is added an 80% NaH suspension (310 mg, 10 mmoles) in tetrahydrofuran (50 mL). The reaction mixture is shacked at room temperature for 1 hour. The resulting solution is then added to a tetrahydrofuran solution containing the imidazolide of the selected alcohol obtained by reacting the alcoholic derivative (10 mmoles) with 1,1'-carbonyl-diimidazole (1.65 g, 10 mmoles) in tetrahydrofuran (20 mL) for 1 hour at room temperature. The mixture is stirred at room temperature for 12 hours, then solvent is take to dryness under vacuum and the residue re-dissolved in methylene chloride.

The organic phase is washed with water, dried by anhydrous Na_2 SO_4 and evaporated under vacuum. The obtained crude material is purified by column

chromatography on silica gel (eluent hexane-ethylacetate, 8:2, v/v). After evaporation of the solvents, the solid pure product obtained is re-dissolved in hexane, filtered and dried under vacuum.

The compounds described below were prepared according to the procedure reported in Example 1.

Example 2

Preparation of 3-(2-(ethoxy-carbonyloxymethyl)phenyl-5-(3-ethoxyphenyl)-1H-1, 2, 4-triazole (XV).

Yield 52%; melting point = 124-126°C

^{1}H-NMR: 7.98 (1H, t, J=4.1 Hz); 7.72-7.74 (6H, m); 7.06 (1H,d, J=6.9 Hz); 5.68 (2H, s); 4.16 (2H, q, J=7.0 Hz), 4.14 (2H, q, J=7.1 Hz); 1.40 (3H, t, J=7.0 Hz); 1.21 (3H, t, J=7.1 Hz).

^{13}C-NMR: 158.76, 154.21, 133.65, 129.83, 129.04, 128.77, 128.60 (2C), 118.16 (2C), 115.86, 112.04 (2C), 67.20, 63.33, 63.15, 14.36, 13.82.

Example 3

Preparation of 3-(2-(butoxy-carbonyloxymethyl)phenyl-5-(3-ethoxyphenyl)-1H-1, 2, 4-triazole (XIV).

Yield 58%; melting point= 119-121°C

^{1}H-NMR: 8.00 (1H, t, J=4.8 Hz); 7.70-7.40 (6H, m); 7.03 (1H,d, J=7.2 Hz); 5.62 (2H, s); 4.12 (2H, q, J=7.0 Hz), 4.03 (2H, t, J=6.4 Hz); 1.49 (2H, m); 1.36 (3H, t, J=7.0 Hz); 1.23 (2H, m); 0.80 (3H, t, J=7.3 Hz).

^{13}C-NMR: 158.70, 154.29, 133.51, 129.89, 129.20 (2C), 128.63 (2C), 128.35 (2C), 118.15 (2C), 115.96, 111.98 (2C), 67.27, 67.17, 63.20, 18.03,14.26, 12.98.

Example 4

Preparation of 3-(2-(hexyloxy-carbonyloxymethyl)phenyl-5-(3-ethoxyphenyl)-1H-1, 2, 4-triazole (XVI).

Yield 42%; melting point = 90-92°C

^{1}H-NMR: 8.07 (1H, m); 7.69-7.40 (6H, m); 7.06 (1H, d, J=7.3 Hz); 5.68 (2H, s); 4.15 (2H, q, J=7.0 Hz), 4.07 (2H, t, J=6.6 Hz); 1.56 (2H, m); 1.40 (3H, t, J=7.0 Hz); 1.23 (6H, m); 0.85 (3H, t, J=6.5 Hz).

^{13}C-NMR: 158.76, 154.29, 133.65, 129.79, 128.87 (2C), 128.59 (2C), 128.15 (2C), 118.15 (2C), 115.87, 112.03 (2C), 67.37, 67.29, 63.13, 30.49, 27.87, 24.52, 21.61,14.36, 13.43.

Example 5

Preparation of 3-(2-(octyloxy-carbonyloxymethyl)phenyl-5-(3-ethoxyphenyl)-1H-1, 2, 4-triazole (XVI).

Yield 49%; melting point= 86-89°C

^{1}H-NMR: 8.06 (1H, m); 7.72-7.40 (6H, m7); 7.05 (1H, d, J=7.1 Hz); 5.69 (2H, s); 4.15 (2H, q, J=7.0 Hz), 4.07 (2H, t, J=6.4 Hz); 1.56 (2H, m); 1.40 (3H, t, J=7.0 Hz); 1.23 (10H, m); 0.86 (3H, t, J=6.5 Hz).

^{13}C-NMR: 158.76, 154.28, 133.65, 129.77, 129.01, 128.84, 128.59 (2C), 128.59 (2C), 128.13 (2C), 118.16 (2C), 115.83, 112.03 (2C), 67.37, 67.30, 63.13, 30.88, 27.91, 24.89, 21.72,14.35, 13.53.

In the following example 6, the synthesis of one derivative of formula (I), where the group R_7 is chosen of formula (XII), symmetric carbonates, is described:

Example 6

Preparation of Di-(2-(5-(3-ethoxyphenyl)-1H-1, 2, 4-triazol-3-yl) phenylmethyl) carbonate (XVII).

A 15 mL solution of 3-(2-(hydroxymethyl)phenyl)-5-(3-ethoxyphenyl)-1H-1, 2, 4 triazole (0.7g, 2.4 mmoles) in tetrahydrofuran, at room temperature, is added a 80% NaH suspension (35 mg, 1.2 mmoles) in tetrahydrofuran (15 mL). The reaction mixture is shacked at room temperature for 1 hour. The resulting solution is then added 1,1'-carbonyl-diimidazole (192 mg, 1.2 mmoles) in tetrahydrofuran (20 mL) for 1 hour at room temperature. The mixture is stirred at room temperature for 12 hours. Solvent is taken to dryness under vacuum and the residue

re-dissolved in methylene chloride. The organic phase is washed with water, dried by anhydrous Na_2 SO_4 and evaporated under vacuum. The obtained crude material is purified by column chromatography on silica gel (eluent hexane-ethylacetate, 7:3, v/v). After evaporation of the solvents, the solid pure product obtained is re-dissolved in hexane, filtered and dried under vacuum. 212 mg of the compound (XVII) are obtained.

Yield 36%; melting point = 143-145°C

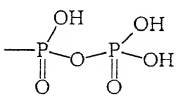
^{1}H-NMR: 8.07 (2H, m), 7.69-7.38 (12H, m); 7.03 (2H,d, J=8.4 Hz); 5.72 (4H, s); 4.12 (4H, q, J=7.0 Hz), 1.37 (6H, t, J=7.0 Hz);.

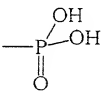
^{13}C-NMR: 158.74, 154.21, 133.59, 129.81 (2C), 128.97 (2C), 128.02 (2C), 118.18 (2C), 115.88, 112.00 (2C), 67.41, 63.13, 14.33.

When R is chosen equal to -CO R_8, where R_8 is a saturated or a non saturated C_1- C_{10} aliphatic hydrocarbon, the hydroxy group of derivative (IX), will be protected according to known methods. Protected derivative (IXb) will be also obtained and acylated according to known methods in order to introduce the -COR_8 group. Subsequently these acylated derivatives will be de-protected and allowed to react with phosgene as

reported above. In the case of X=Y=N, the acylation reaction could be carried out as described by EP80053.

When R_5 is chosen:





Derivatives of formula (I) are advantageously prepared starting from derivatives of formula (IX) (eventually submitted to a previous acylation reaction as already described) by reaction with phosphoric acid or equivalents according to known methods. For example, following this procedure derivative (VIII), object of the present invention, is prepared..

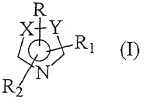
For derivatives of formula (I), when X=Y=N and R=H, following the acylation procedure described above, both single compounds, where the substituent R is located on one of the two adjacent nitrogen atoms and mixtures of the two possible isomers can be obtained.

In this latter case, being established that each isomer retains the same anti-gestative immuno-suppressant and anti tumour activity, the mixture can be separated into the single components by chemico-physical known methods. For example, the way a mixture can be resolved into the single components is a fractionated crystallisation,

which take advantage of the different solubility of each compound in various solvents at different temperatures. Suitable solvents that can be used for this method are chosen as an example, among hexane, ethyl-acetate, C_1-C_4 alkyl ethers, methylen chloride, light petroleum ether and mixtures thereof. A further illustrative example of a method useful for the separation of the isomers' mixture is based on column chromatography, performed on non-acid, buffered adsorbents, as silica-gel buffered to ph=7. Another example of a method useful for the separation of the isomer mixture is based on the use of preparative high pressure liquid chromatography (PHPLC), carried out on proper columns, for example filled with silica-gel esterified with octyl-silane or octyl-decylsilane. Other obvious procedures useful for resolving a mixture of isomers into the single components are intended to fall within the scopes of the invention.

CLAIMS

1.Nitrogen heterocyclic aromatic derivatives having the following general formula:



(I)

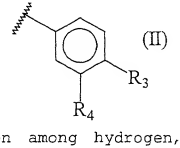
where:

-when X=Y, X, Y=N;

-when X≠Y, X, Y=N, C, CH;

-R is chosen between hydrogen, -COR8 where R8 is a saturated or non-saturated aliphatic hydrocarbon C1-C10, or R represents any other group able to form a bond with a nitrogen atom;

- R1 has the following general formula:

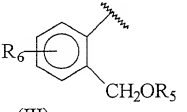


(II)

where R3 is chosen among hydrogen, halogen, alkyl or alkoxyl C1-C10, R4 is chosen among hydrogen, alkyl or alkoxyl C1-C10, or R3 and R4 together form a methylendioxy group;

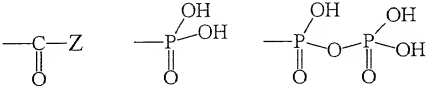
AMENDED SHEET

- R_2 has the following general structure:

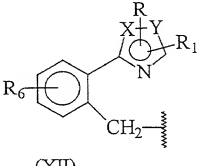


(III)

where R_5 is chosen among:



where $Z=OR_7$ with R_7 is chosen among a saturated or non-saturated, linear or branched C_1-C_{20} aliphatic hydrocarbon, or is chosen according to the following formula:



(XII)

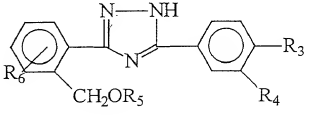
where R, R_1, X and Y are defined as above and R_6 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, or Z is chosen equal to NHR_8 where R_8 is a linear or branched C_1-C_{20} alkyl chain, provided that:

when X=Y=N and R is chosen equal to H or to $-CONHCH_2CH_3$, Z is different from NHR_8 where R_8 is equal to $-CH_2CH_3$. Mentioned R_1 and R_2 are never located on two adjacent atoms of the heterocyclic aromatic ring.

2.Nitrogen heterocyclic aromatic derivatives according to the claim 1. characterised by a saturated or non-saturated C1- C_{20} aliphatic hydrocarbon represented by a linear or branched alkyl, alkenyl or alkinyl which can contain one or more double or triple bonds. Always according to the present invention, the term alkyl or alkoxyl means a linear or branched C_1-C_{10} alkyl or alkoxyl group.

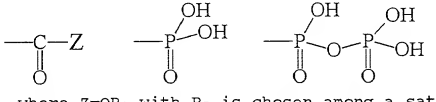
3.Nitrogen heterocyclic aromatic derivatives according to the claim 1. characterised by the fact that are derivatives of imidazole and 1H-1, 2, 4-triazole respectively:

4.Nitrogen heterocyclic aromatic derivatives according to the claim 1, characterised by having X=Y=N, R=H and showing the following general formula:

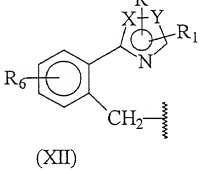


(IV)

where R_3 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, R_4 is chosen among hydrogen, alkyl or alkoxyl C_1-C_{10}, or R_3 and R_4 together form a methylendioxy group, where R_5 is chosen among:



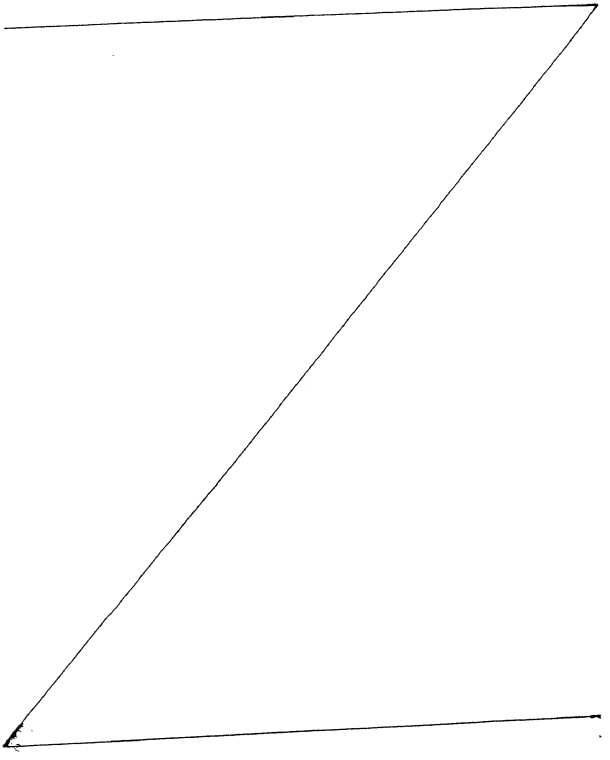
where Z=OR_7 with R_7 is chosen among a saturated or non-saturated, linear or branched C_1-C_{20} aliphatic hydrocarbon, or is chosen according to the following formula:



(XII)

AMENDED SHEET

where R, R_1, X and Y are defined as above and R_6 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10},

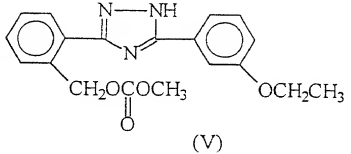


AMENDED SHEET

or Z is chosen equal to NHR_8 where R_8 is a linear or branched C_1-C_{20} alkyl chain.

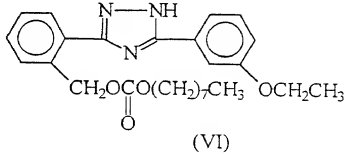
5. Nitrogen heterocyclic aromatic derivatives according to claim 4. characterised by having R_6 = hydrogen, R_4 = OCH_3 or OCH_2CH_3. Mentioned R_3 is hydrogen, mentioned R_5 is chosen equal to COZ where Z=OR_7 with R_7 as a saturated linear aliphatic C_1-C_{12} hydrocarbon.

6. Nitrogen heterocyclic aromatic derivative according to claim 1. having the following chemical structure:



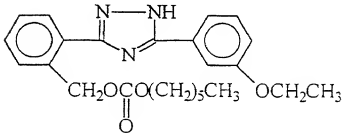
(V)

7. Nitrogen heterocyclic aromatic derivative according to claim 1. having the following chemical structure:



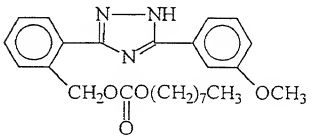
(VI)

8.Nitrogen heterocyclic aromatic derivative according to claim 1. having the following chemical structure:



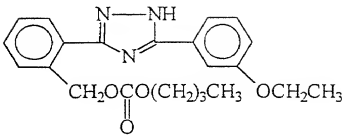
(XVI)

9. Nitrogen heterocyclic aromatic derivative according to claim 1.having the following chemical structure:



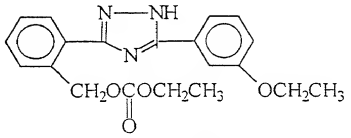
(XIII)

10.Nitrogen heterocyclic aromatic derivative according to claim 1. having the following chemical structure:



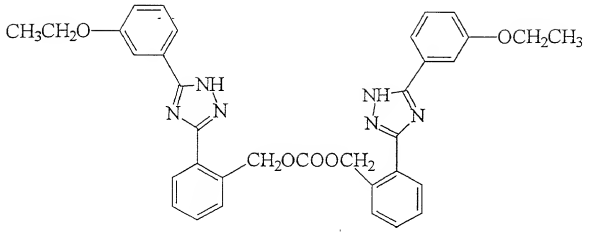
(XIV)

11.Nitrogen heterocyclic aromatic derivative according to claim 1. having the following chemical structure:



(XV)

12.Nitrogen heterocyclic aromatic derivative according to claim 1.having the following chemical structure:



(XVII)

13.Nitrogen heterocyclic aromatic derivatives, according to claim 1., for use as a medicament.

14.Nitrogen heterocyclic aromatic derivatives, according to claim 1, for use as a medicament

15. Use of the nitrogen heterocyclic aromatic derivatives, according to claim 1., for the preparation of a drug with anti-gestative activity.

16.Use of the nitrogen heterocyclic aromatic derivatives, according to claim 1., for the preparation of a drug with immuno-suppressant activity.

17. Pharmaceutical composition with anti-gestative action which contains at least one nitrogen heterocyclic aromatic derivative, according to claim 1., as active principle.

18. Pharmaceutical composition with immuno-suppressant action which contains at least one nitrogen heterocyclic aromatic derivative, according to claim 1., as active principle.

19. Pharmaceutical composition according to claims 17 and 18., formulated utilising systems suitable for a transdermic release.

20. Pharmaceutical composition according to claims 17 and 18., formulated utilising proper aqueous systems suitable for an intravenous administration.

21. Pharmaceutical composition according to claim 17 and 18., formulated utilising vegetable oils or esters of fatty acids, i.e, sesame oil, suitable for an epicutaneous, subcutaneous and intramuscular administration.

22. Pharmaceutical composition according to claim 21., formulated utilising oils of vegetable origin or fatty esters such as sesame oil, corn oil, peanut oil, cotton seed oil, and ethyl oleate.

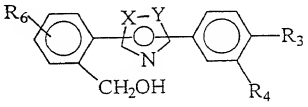
23. Pharmaceutical composition according to claim 17 and 22., formulated utilising previously disclosed anti-microbic agents

24. Pharmaceutical composition according to claim 17 and 22., formulated utilising previously disclosed anti-oxidative agents.

25. Pharmaceutical composition according to claim 17 and 24., containing from 1 to 10 % (w/v) of at least one nitrogen heterocyclic aromatic derivative according to claim 1.

26. Method of preparation of nitrogen heterocyclic aromatic derivative according to claim 1, which involves the following synthesis phases:

a) preparation of one nitrogen heterocyclic aromatic derivative of general formula

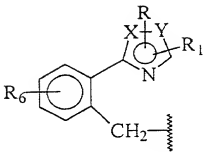


(IX)

b) possible protection of the OH group, possible acylation reaction with introduction of a $-COR_8$ group leading to the formation of an acylated derivative, subsequent de-protection of the OH group, and alternatively:

c) reaction of derivative (IX) with a carbonatante agent, to give rise to a corresponding carbonate product.

d) reaction of the above mentioned carbonate with Z to obtain the mentioned derivative (I). Where $Z=OR_7$ with R_7 is chosen among a saturated or non-saturated, linear or branched C_1-C_{20} aliphatic hydrocarbon, or is chosen according to the following formula:



(XII)

where R, R_1, X and Y are defined as above and R_6 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, or Z is chosen equal to NHR_8 where R_8 is a linear or branched C_1-C_{20} alkyl chain;

or: reaction of the above mentioned derivative (IX) with phosphoric acid or equivalent products, with formation of the derivative of formula (I).

27. Procedure according to claim 26, characterised by selecting as carbonatante agent phosgene ($COCl_2$).

Case No. 8 I P E

JAN 2 8 2000

Nixon & Vanderhye P.C. (12/97)

RULE 63 (37 C.F.R. 1.63)
DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

the specification of which (check applicable box(s)):

☐ ** is attached hereto
☐ * was filed on _____ as U.S. Application Serial No. _____
☐ was filed as PCT international application No. _____ on _____
and (if applicable to U.S. or PCT application) was amended on _____

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed or, if no priority is claimed, before the filing date of this application:

Priority Foreign Application(s):

Application Number	Country	Day/Month/Year Filed

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

Application Number	Date/Month/Year Filed

I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior applications in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.56 which occurred between the filing date of the prior applications and the national or PCT international filing date of this application:

Prior U.S./PCT Application(s):

Application Serial No.	Day/Month/Year Filed	Status: patented pending, abandoned

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. And I hereby appoint NIXON & VANDERHYE P.C., 1100 North Glebe Rd., 8th Floor, Arlington, VA 22201-4714, telephone number (703) 816-4000 (to whom all communications are to be directed), and the following attorneys thereof (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent: Arthur R. Crawford, 25327; Larry S. Nixon, 25640; Robert A. Vanderhye, 27076, James T. Hosmer, 30184; Robert W. Faris, 31352; Richard G. Besha, 22770; Mark E. Nusbaum, 32348; Michael J. Keenan, 32106; Bryan H. Davidson, 30251; Stanley C. Spooner, 27393; Leonard C. Mitchard, 29009; Duane M. Byers, 33363; Jeffry H. Nelson, 30481; John R. Lastova, 33149; H. Warren Burnam, Jr. 29366; Thomas E. Byrne, 32205; Mary J. Wilson, 32955; J. Scott Davidson, 33489; Alan M. Kagen, 36178; William J. Griffin, 31260; Robert A. Molan, 29834; B. J. Sadoff, 36663; James D. Berquist, 34776, Updeep S. Gill, 37334.

1. Inventor's Signature: Carla Rossi Date: 1-00

Inventor:	(first) CARLA	MI	(last) ROSSI	(citizenship) ITALIAN
Residence: (city)	MILAN		(state/country) ITALY	
Post Office Address:				
(Zip Code)				

2. Inventor's Signature. _____ Date: _____

Inventor:	(first)	MI	(last)	(citizenship)
Residence: (city)			(state/country)	
Post Office Address:				
(Zip Code)				

3. Inventor's Signature: _____ Date: _____

Inventor:	(first)	MI	(last)	(citizenship)
Residence: (city)			(state/country)	
Post Office Address:				
(Zip Code)				

FOR ADDITIONAL INVENTORS, check box ☐ and attach sheet with same information and signature and date for each.